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(57) Abstract

The object of the present invention is a pharmaceutical composition, characterised in that it comprises, as active principle, a combination of an adenosinergic agonist and a compound selected from the opiates, benzodiazepines and NMDA antagonists. Application: treatment of pain.

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PHARMACEUTICAL COMBINATION WITH ANALGESIC ACTIVITY, CONTAINING AN ADENOSINERGIC AGONIST AND A COMPOUND SELECTED FROM OPIATES, BENZODIAZEPINES AND NMDA ANTAGONISTS

The object of the present invention is a novel pharmaceutical combination which especially finds application in the treatment of various types of pain which can be of inflammatory origin or neuropathic origin. More specifically, the invention relates to a pharmaceutical composition which comprises, as active principle, a combination of an adenosinergic agonist and a compound selected from the opiates, benzodiazepines and NMDA antagonists.

It is known that adenosine is an endogenous molecule which participates in the regulation of many functions, in the central nervous system and peripherally, via the activation of specific receptors (Daly, I.W. in: T.W. Stone (Ed.) Purines Pharmacological and Physiological Roles, Macmillan, London. 1985: pp. 5-15).

The inhibitory role of adenosine in the modulation of the transmission of the pain message is now well-establishcd (Sawynok, J., M.I. Sweeney. Neurosci. 1989;(32):557-569).

Many pharmacological studies have demonstrated the analgesic activity of adenosine and its analogues (M., Holmgrcn, J. Hedner, T. Mellstrand, G. Nordberg, Th. Hedner. Naunym-Schmicdeberg's Arch. Pharmacol. 1986; (334):290-293 ; and K., Herrick-Davis, S. Chippari, D. Luttinger, S.J. Ward. Eur. J. Pharmacol. 1989; 162 :365-369.

However, for the majority, these compounds induce, at active doses, nonnegligible side effects, in particular cardiovascular side effects, which have hitherto limited the use of them.

Research has enabled developing adenosinergic agonist compounds which are active in animal acute or chronic pain models and which are devoid of major side effects at active doses.

Such compounds have for example been described in the document EP 623138 by the Applicant company.

Furthermore, it is known that opiate or morphinic compounds are powerful centrally acting analgesics which are indicated in the treatment of moderate to severe pain. These compounds can however induce tolerance and dependence in certain circumstances.

It is further known that benzodiazepines possess anxiolitic, muscle relaxing, anti-convulsivant and hypnotic properties.

Finally, it is known that the activation of N-methyl-D-aspartate (NMDA) receptors by neuro-excitatory amino acids (aspartate, glutamate) is implicated in certain pain processes.

NMDA antagonists thus possess an analgesic activity which is demonstrated in many tests, including chronic pain tests.

It has been discovered, and this constitutes the basis of the present invention, that the combination of an adenosinergic agonist and a compound selected from the opiates, benzodiazepines and NMDA antagonists, possesses a significant analgesic effect at doses at which each one of the products constituting this combination is inactive or not very active.

The beneficial effect of the combination in accordance with the present invention has been demonstrated both in inflammatory pain models and in noninflammatory acute pain models.

The results obtained have shown that this combination possesses an analgesic activity very much greater than that of each one of its constituent products used alone at the same dose.

The potentiation effect thus demonstrated renders the use of low doses of each one of the constituent products of the combination possible, thereby limiting their possible side effects, and increasing their therapeutic index. Moreover, this combination enables treating pain of very varied origin in a larger number of patients.

Advantageously, the pharmaceutical combination in accordance with the present invention will be in a form suitable for an administration:

- via the oral route, such as simple or coated tablets, capsules or granules, for example;

- via the rectal route, such as suppositories for example

- via the parenteral route, such as injectable preparations for example

- via the ocular route, such as eye lotions or ophthalmic solutions for example;

- via the transdermal route, such as a patch, an ointment or a gel for example;

- via the nasal route, such as aerosols and sprays for example; or

- via the auricular route, such as drops for example.

Such a composition can be prepared, according to the methods known per *se*, by incorporating the active principle, consisting of the above-mentioned combination, with excipients usually used such as talc, gum arabic, lactose, starch, magnesium stearate, polyvidone, cellulose derivatives, cocoa butter, semi-synthetic glycerides, aqueous or non-aqueous vehicles, fats of animal or vegetable origin, glycols, wetting agents, dispersing agents or emulsifiers, silicone gels, certain polymers or co-polymers, preservatives, flavours and colouring agents.

In general, any adenosinergic agonist compound can be used within the context of the present invention. Preferably, adenosine derivatives will be used such as those described in the document
EP 233138 which corresponds to US patents 5,229,505 and 5,480,983 of the Applicant company which are incorporated herein by reference.

A particularly preferred compound is N-cyclopropyl-l-deoxy-l-[6-[[2-[l[(2,5-dimethylphenyl)methyl]-5-methyl-lH-indol-3-yl]ethyl]amino]-9H-purin-9-yl]β-D-ribofuranuronamide, known under the code name UP 202-56.

Another particularly preferred compound is N-cyclopropyl-l-deoxy-l-[6[[2-[1-[2-(l-piperidinyl)ethyl]-lH-indol-3-yl]ethyl]aminol-9H-purin-9-yl]β-D-ribo-furanuronamide, known under the code name UP 202-39.

Opiates which can be used within the context of the present invention can be of different nature: powerful opiates, of which the top of the pile is morphine, which can treat severe pain, such as morphine itself or oxycodonc or hydromorphone or hydrocodone, or weak opiates, which can treat pain of moderate intensity, such as codeine or dextropropoxyphen.

Derivatives having a powerful central analgesic effect will more particularly be preferred, morphine itself in particular.

The benzodiazepines which can be used within the context of the present invention can be of various nature such as prazepam, bromazepam, chlordiazepoxide, lorazepam or clobazam.

Diazepam will more particularly be preferred.

Dextrometorphan, ketamine, dizocilpine or phencyclidine will be cited in particular amongst the NMDA antagonists which can be used within the context of the present invention.

Dextrometorphan will more particularly be preferred.

Advantageously, the pharmaceutical compositions according to the invention will be presented in the form of a unit dose.

In the pharmaceutical combination in accordance with the present invention, the weight ratio of the adenosinergic agonist compound to the compound selected from the opiates, benzodiazepincs and NMDA antagonists, will be that which has the best synergy between the two compounds combined. For the majority of the examples, it will be between 0.01 and 10, and will preferably be between 0.1 and 1.

The daily dose which can be employed of the various compounds which constitute the pharmaceutical combination in accordance with the invention will of course depend upon the state of the patient to be treated.

A suitable daily dose of adenosincrgic agonist compound will generally be between about 10 mg and about 500 mg.

The pharmaceutical compositions in accordance with the present

invention are suitable for the treatment of pain of inflammatory origin or of neuropathic origin.

Their use can for example be cited in the treatment of arthritis, especially rheumatoid arthritis, spondylitis, gouty arthritis, ostcoarthritis, juvenile arthritis, autoimmune diseases and lupus erythematosus.

These compositions can also be used within the context of the treatment of bronchial asthma, dysmenorrhea, tendinitis, bursitis, dermatological inflammations such as psoriasis, eczema, burnss and dermatitis.

These compositions can also be used within the context of the treatment of gastrointestinal inflammations, Crohn's disease, gastritis and ulcerative colitis; in the prevention of cancer, especially adenocarcinoma of the colon; in the prevention of neurodegenerative diseases, particularly Alzheimer's disease; in the prevention of stroke and epilepsy, and in the prevention of premature labour.

These compositions can be used within the context of the treatment of pain symptoms, and especially in the treatment of myalgia or articular pain, dental pain, migraine, rheumatic complaints, pain of cancerous origin, and also as complementary treatments for infectious and febrile states.

Finally, these compositions can be used within the context of the treatment of neuropathic pain and in particular neuralgia, herpes, deafferentation pain, and diabetic neuropathies.

The invention even covers a method of therapeutic treatment of mammals, characterised in that it consists in administering to said mammal a therapeutically effective amount of a combination of an adenosinergic agonist compound and a compound selected from the opiates, benzodiazepines and NMDA antagonists as defined above.

This method especially enables treating pain of inflammatory or neuropathic origin.

Description of the Drawings

Figure 1 graphically illustrates the antinociceptive effect of intraperitoneal UP 202-39 and morphine combination in the hot plate test (56 °C) in mice; Dunnett's test * and *** indicate a significant difference in comparison to the control group for $p<0.05$ and $p<0.01$, respectively. Student's test ++ and +++ indicate a significant difference between the combination and the morphine group for $p<0.01$ and $p<0.001$, respectively. °° and °°° indicate a significant difference between the combinatin and the UP-202-39 group for $p<0.01$ and $p<0.001$, respectively. n = 10 per group;

Figure 2 graphically illustrates the antinociceptive effect of UP 202-56 and morphine combination in the hot plate test (56 °C) in mice; Dunnett's test *, ** and *** indicate a significant difference in comparison to the control group for $p<0.05$, $p<0.01$ and $p<0.001$, respectively. Student's test +++ indicates a significant difference between the combination and the morphine group for $p<0.001$. °° and °°° indicate a significant difference between the combinatin and the UP-202-56 group for $p<0.01$ and $p<0.001$, respectively. n = 10 per group;

Figure 3 graphically illustrates the effect of diazepam (10 mg/kg i.p.) on UP 202-39-induces antinociception in the hot plate test (56 °C) in mice; Dunnett's test * and *** indicates a significant difference in comparison to the control group for $p<0.05$ and $p<0.001$, respectively. n = 10 per group.

Figure 4 graphically illustrates the effect of diazepam (10 mg/kg i.p.) on UP 202-56-induced antinociception in the hot plate test (56 °C) in mice; Dunnett's test ** and *** indicates a significant difference in comparison to the control group for $p<0.01$ and $p<0.001$, respectively. n = 10 per group.

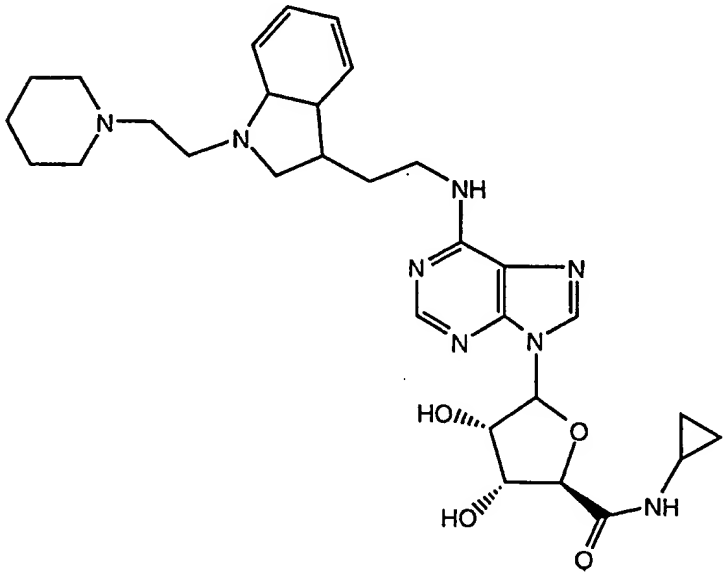
Figure 5 graphically illustrates the effect of dextromethorphan (30 mg/kg i.p.) on UP 202-39-induced antinociception in the hot plate test (56 °C) in mice. Dunnett's test *** indicates a significant difference in comparison to the control group for $p<0.001$. n = 10 per group.

Demonstration of the analgesic properties of the pharmaceutical combination in accordance with the invention.

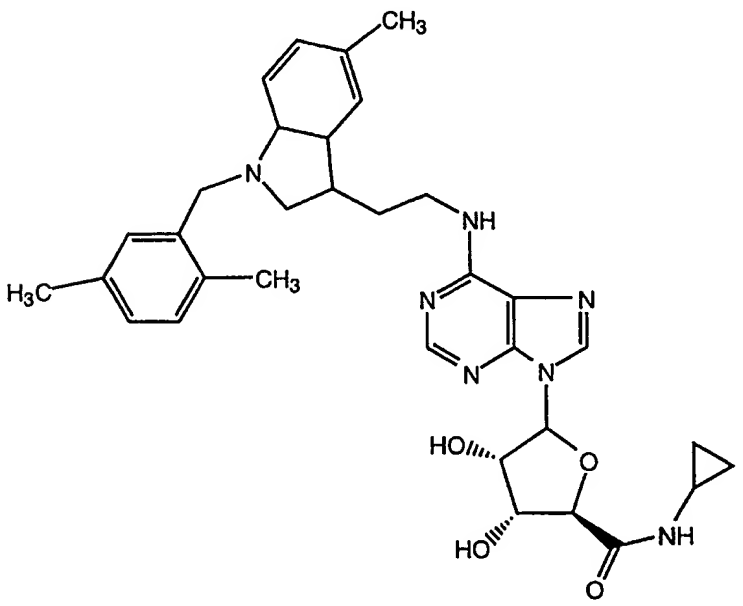
In order to demonstrate the specific analgesic properties of the pharmaceutical combination in accordance with the present invention, several pharmacological tests have been performed whose experimental protocols and results obtained are given below.

In these tests, the compounds used as examples of an adenosinergic agonist are the compounds known :

- under the code name UP 202-39 having the following general formula :



- under the code name UP202-56 having the following general formula :



Test used: Heated Plate Test

The test is carried out by following the experimental protocol described by N.B. Eddy, C.F. Toucheberry and J.E. Uebemian, Synthetic Analgesics, 1-Methadone Isomers and Derivatives, J. Pharmacol. Exp. Ther. 1950 ; (98) : 121-137.

The mouse disposed on a plate heated to 56 °C ± 0.05 shows its pain by licking its front paws, or more rarely by a jump.

The reaction time is then noted down, the maximum time being 30 seconds.

The compounds or combinations studied are administered via the oral route or via the intraperitoneal route one hour or thirty minutes respectively before the test.

The results obtained are represented in Figures 1 to 5 which clearly show the potentiation effect exerted by morphine (FIG. 1 and 2), by diazepam

(FIG. 3 and 4) upon the adenosinergic agonist compounds UP 202-39 and UP 202-56, as well as by dextrometorphan upon the compound UP 202-39.

Several examples of pharmaceutical compositions according to the invention are now given :

EXAMPLE 1: UP 202-56/DEXTROMFTORPRAN COMBINATIONS

Example 1A : Capsule (size no. 1) .

UP 202-56.....10 mg
Dextrometorphan.....20 mg
Microcrystalline cellulose.....100 mg
Hydroxypropyl methyl cellulose.....10 mg
Magnesium stearate.....5 mg for a capsule

Example 1B : Tablet

UP 202-56.....10 mg
Dextrometorphan.....20 mg
Microcrystalline cellulose.....100 mg
Lactose.....100 mg
Hydroxypropyl methyl cellulose.....10 mg
Magnesium stearate.....5 mg
Hydroxypropyl cellulose.....50 mg for a tablet

Example 1C : Suppository

UP 202-56.....20 mg
Dextrometorphan.....40 mg
Semi-synthetic glyceride (suppocire)..1,900 mg for a suppository

Example 1D : Ophthalmic solution

UP 202-56.....0.03%
Dextrometorphan.....0.06%
Castor oil (Cremophor EL).....5.%
Polysorbate 80.....1.%
Water preparation for injections.....q.s.p.100 %

Example 1E : Injectable preparation

UP 202-56.....0.03 %
Dextrometorphan.....0.06 %
PEG 400.....40 %
Ethyl alcohol.....10 %
Water preparation for injection q.s.p.....100 %

EXAMPLE 2: UP 202-56/DIAZEPAM COMBINA'TTONS

Example 2A : Capsule (size no. 1)

UP 202-56 ..... 10 mg
Diazepam ..... 10 mg
Microcrystalline cellulose ..... 100 mg
Hydroxypropyl methyl cellulose ..... 10 mg
Magnesium stearate ..... 5 mg for a capsule

Example 2B : Tablet

UP 202-56 ..... 10 mg
Diazepam ..... 10 mg
Microcrystalline cellulose ..... 100 mg
Lactose ..... 100 mg
Hydroxypropyl methyl cellulose ..... 10 mg
Magnesium stearate ..... 5 mg
Hydroxypropyl cellulose ..... 50 mg for a tablet

Example 2C: Suppository

UP 202-56 ..... 20 mg
Diazepam ..... 20 mg
Semi-synthetic glyceride (suppocire) ..... 1,920 mg for a suppository

Example 2D : Ophthalmic solution

UP 202-56 ..... 0.03 %
Diazepam ..... 0.03 %
Castor oil (Cremophor EL) ..... 5 %
Polysorbate 80 ..... 1 %
Water preparation for injection ..... q.s.p.100 %

Example 2E : Injectable preparation

UP 202-56 ..... 0.03 %
Diazcpam ..... 0.03 %
PEG 400 ..... 40 %
Water preparation for injections ..... q.s.p.100 %

EXAMPLE 3: UP 202-56/MORPHINE SULPHATE COMBINATIONS

Example 3A : Capsule (size no. 1)

UP 202-56.....10 mg
Morphine sulphate.....10 mg
Microcrystalline cellulose.....100 mg
Hydroxypropyl methyl cellulose.....10 mg
Magnesium stearate.....5 mg for a capsule

Example 3B: Tablet

UP 202-56.....10 mg
Morphine sulphate.....10 mg
Microcrystalline cellulose.....100 mg
Lactose.....100 mg
Hydroxypropyl methyl cellulose.....10 mg
Magnesium stearate.....5 mg
Hydroxypropyl cellulose.....50 mg for a tablet

Example 3C : Suppository

UP 202-56.....20 mg
Morphine sulphate.....20 mg
Semi-synthetic glyceride (suppocire).....1.920 mg for a suppository

Example 3D : Ophthalmic solution

UP 202-56.....0.03 %
Morphine sulphate .....0.03 %
Castor oil (Cremophor EL).....5 %
Polysorbate 80.....1%
Water preparation for injections.....q.s.p.100 %

Example 3E : Injectable preparation

UP 202-56..... 0.03 %
Morphine sulphate..... 0.03 %
PEG 400..... 40 %
Ethyl alcohol.....10 %
Water preparation for injections q.s.p..... 100 %

CLAIMS

1. A pharmaceutical composition,. characterised in that it comprises, as active principle, a combination of an adenosinergic agonist and a compound selected from the opiates, benzgdiazepines and NMDA antagonists.

2. The pharmaceutical composition according to claim 1, characterised in that the above-mentioned adenosinergic agonist compound is selected from Ncyclopropyl-l-de oxy-l-[6-[[2-[I-[.)-(l-piperidinyl)ethyl]-lH-indol-3yl]ethyl]-amino]-9H-purin-9-yl] P-D-ribofuranuronamide, known under the10 code name UP 202-39 and N-cyclopropyl-i-deoxy-l-[6-[[2-[I-[(2,5-dimethylphenyl)-mcthyl]-5-methyl-lH-indol-3-yl]cthyl]amino]-9H-purin-9yl] β-D-ribofuranuron-amide, known under the code name UP 202-56.

3. The pharmaceutical composition according to claim 1 or 2, characteriscd in that the abovc-mentioned opiate compound is morphine.

4. The pharmaceutical composition according to claim 1 or 2, characterised in that the above-mentioned benzodiazepine is diazepam.

5. The pharmaceutical composition according to claim 1 or 2, characterised in that the NMDA antagonist compound is dcxtrometorphan.

6. Thne pharmaceutical composition according to one of claims 1 to 5, characterised in that it is in a form suitable for administration via the oral route, via the parenteral route, via the rectal route, via the ocular route, via the transdennal route, via the nasal route, or via the auricular route.

7. The pharmaceutical composition according to one of claims 1 to 6, characterised in that the weight ratio of the adenosinergic agonist compound to the compound selected from the opiates, benzodiazepines and NMDA antagonists, is selected in order to lead to the best synergy between the two compounds combined, and is preferably between about 0.01 and about 10 and will be preferably still between 0.1 and 1.

8. The pharmaceutical composition according to one of claims 1 to 7, characterised in that it is in the form of a unit dose containing from 5 mg to 200 mg of adenosinergic agonist compound.

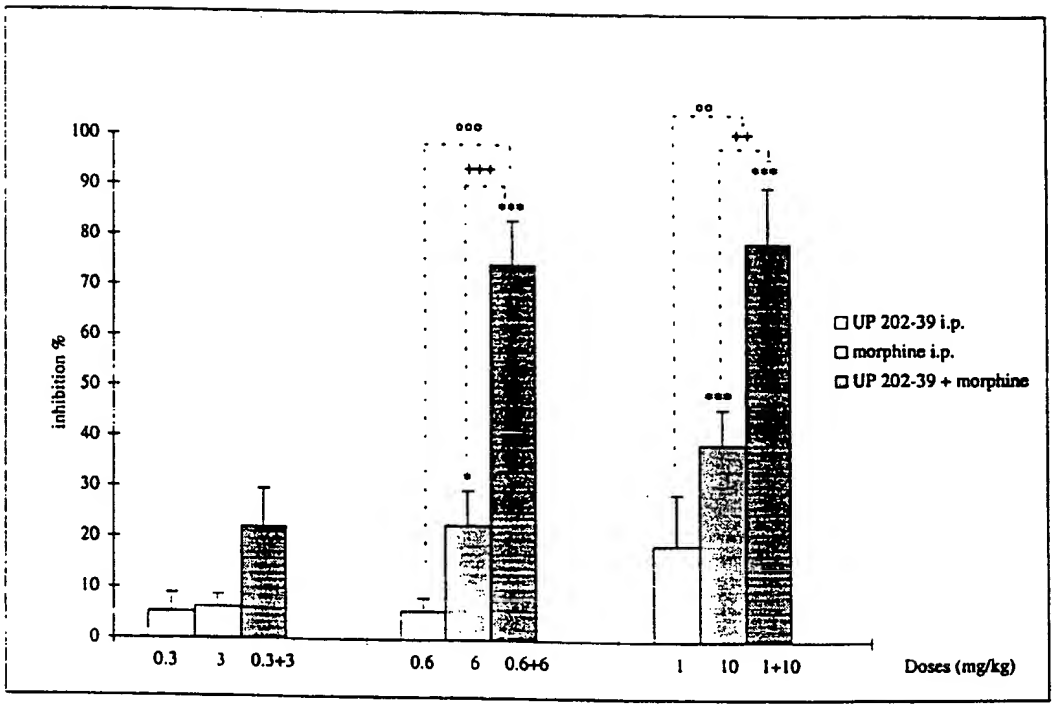

inhibition %
100
90
80
70
60
50
40
30
20
10
0
0.3
3
0.3+3
0.6
6
0.6+6
1
10
1+10
Doses (mg/kg)
UP 202-39 i.p.
morphine i.p.
UP 202-39 + morphine

Figure 1

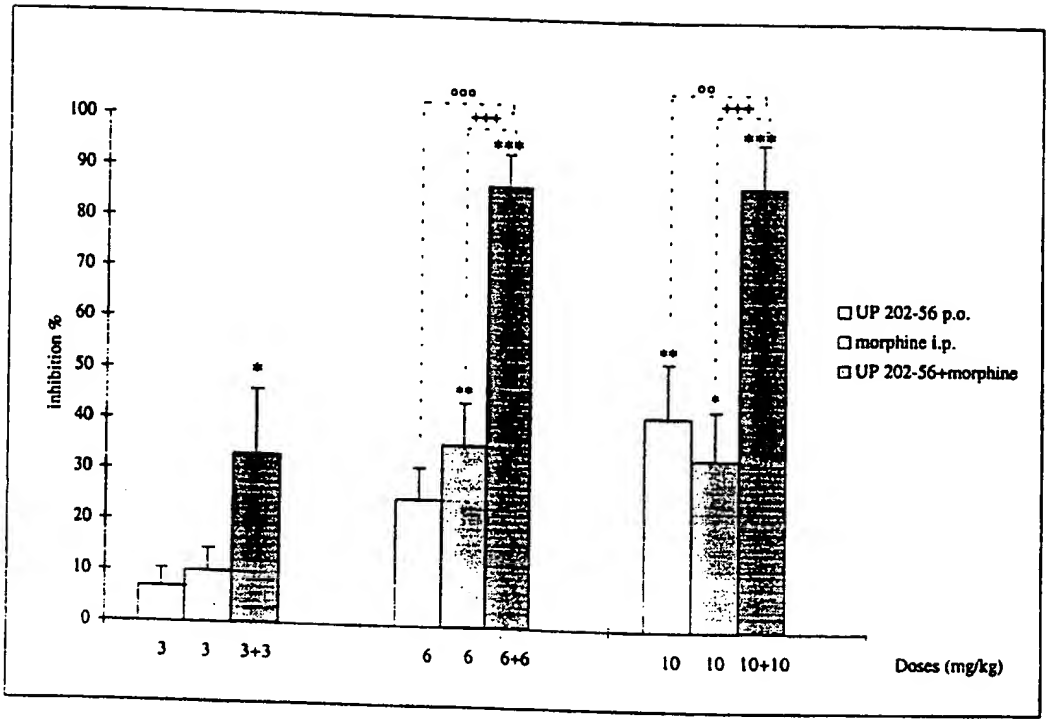

inhibition %
100
90
80
70
60
50
40
30
20
10
0
3
3
3+3
6
6
6+6
10
10
10+10
Doses (mg/kg)
UP 202-56 p.o.
morphine i.p.
UP 202-56+morphine

Figure 2

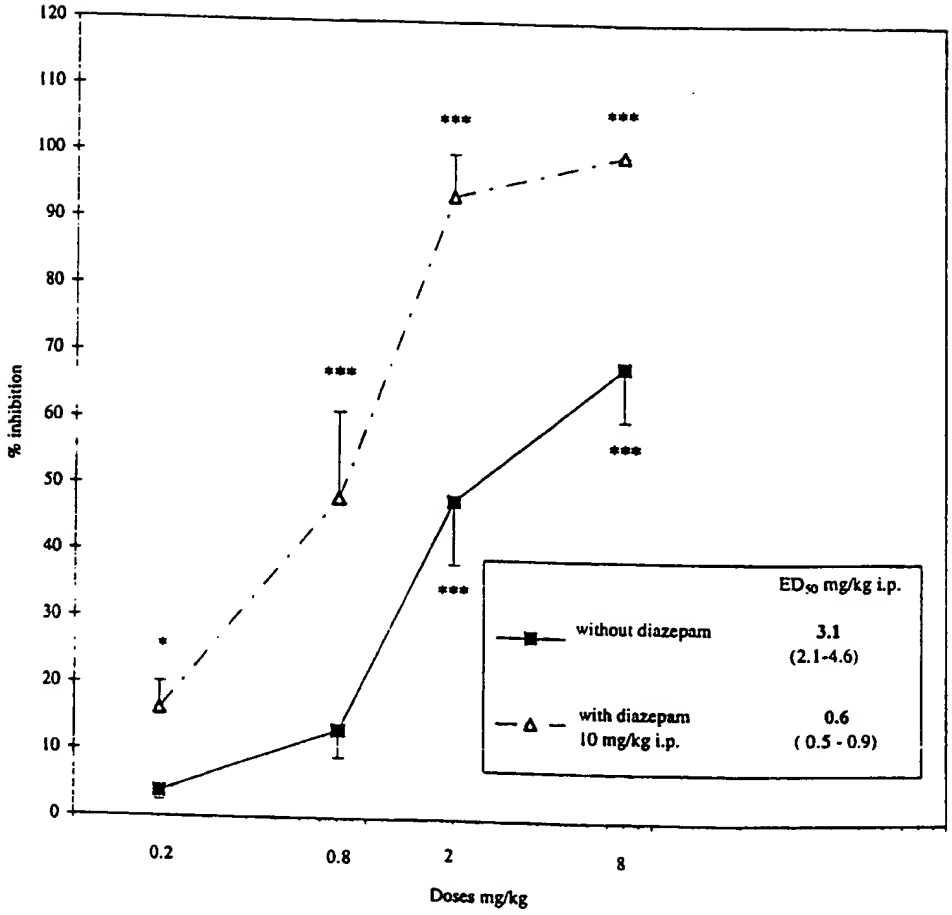

120
110
100
90
80
70
60
50
40
30
20
10
0
% inhibition
0.2
0.8
2
8
Doses mg/kg
*
***
***
***
***
***
ED50 mg/kg i.p.
without diazepam
3.1
(2.1-4.6)
with diazepam
10 mg/kg i.p.
0.6
(0.5 - 0.9)

Figure 3

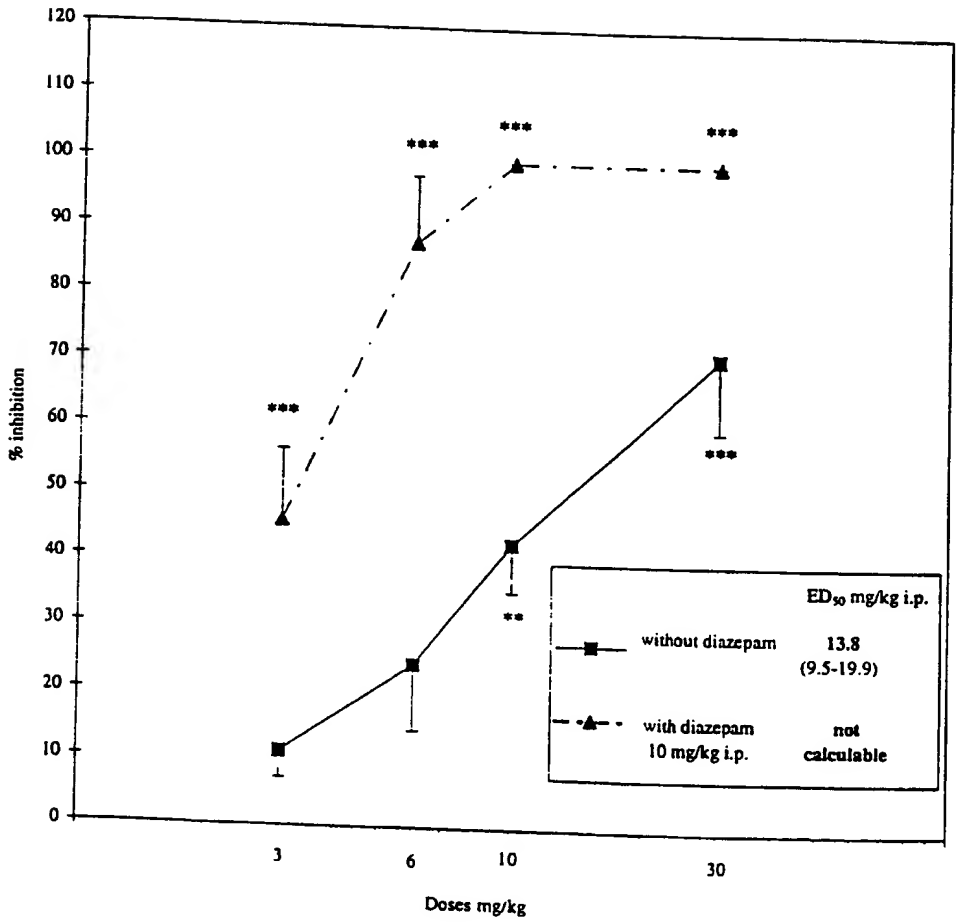

120
110
100
90
80
70
60
50
40
30
20
10
0
% inhibition
***
***
***
***
***
**
3
6
10
30
Doses mg/kg
ED50 mg/kg i.p.
without diazepam
13.8
(9.5-19.9)
with diazepam
10 mg/kg i.p.
not
calculable

Figure 4

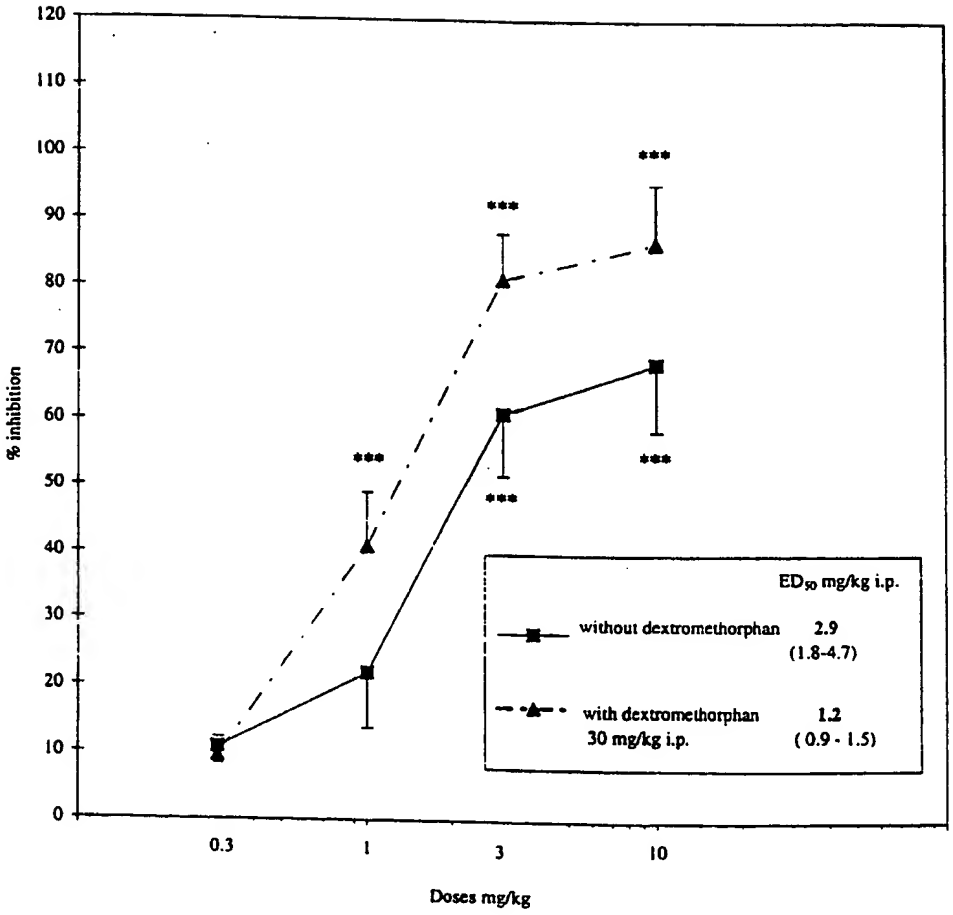

120
110
100
90
80
70
60
50
40
30
20
10
0
% inhibition
0.3
1
3
10
Doses mg/kg
***
***
***
***
***
ED50 mg/kg i.p.
without dextromethorphan 2.9
(1.8-4.7)
with dextromethorphan 1.2
30 mg/kg i.p. (0.9 - 1.5)

Figure 5

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/EP 98/08164

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K45/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE BIOSIS BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US CONTRERAS E ET AL: "EFFECTS OF SOME ADENOSINE ANALOGS ON MORPHINE-INDUCED ANALGESIA AND TOLERANCE" XP002077489 see abstract & GEN PHARMACOL, 21 (5). 1990. 763-768., --- -/--	1,3,6

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
11 May 1999	19/05/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Leherte, C

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INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/EP 98/08164

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